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**NEW UTILITY PATENT APPLICATION
TRANSMITTAL
(Small Entity)**

(Only for new nonprovisional applications under 37 C.F.R. 1.53(b))

Docket No. P52.2-7161

Total Pages in this Submission
(including checks and postcard)

1c551 U.S. PTO
09/11/98

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled: COMPOSITION FOR CREATING VASCULAR OCCLUSIONS

and invented by: Robert E. Krall, Charles Kerber and Kimberly Knox

If a CONTINUATION APPLICATION, check appropriate box and supply the requisite information:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: ____

Enclosed (in addition to the 4 pages of this transmittal) are:

4 pages

Application Elements

1. ☒ **Filing fee as calculated below:**
a ☒ filing fee is NOT ENCLOSED - fee will be paid at the time of responding to Notice of Missing Parts - DO NOT CHARGE DEPOSIT ACCOUNT
b. ☐ a check in the amount of \$ _____ to cover the filing fee is enclosed.
c. ☐ charged to Deposit Account as authorized in item 2(a) below _____ pages

FEE CALCULATION AND CLAIMS					
For	No. Filed	No. Allowed	No. Extra	Rate	Fee
Total Claims	6	- 20 =		x \$11.00	\$
Indep. Claims	2	- 3 =		x \$41.00	\$
BASIC FEE					\$ 395.00
TOTAL FILING FEE					\$395.00

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2. The Commissioner is hereby authorized to charge and credit Deposit Account No. 22-0350 as described below. A duplicate copy of this sheet is enclosed. _____ page
- a. ☐ Charge the amount of \$_____ as filing fee.
 - b. ☐ Credit any overpayment.
 - c. ☐ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
 - d. ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).
3. ☒ Specification having 6 pages and including the following: _____ pages
- a. ☒ Application Cover Sheet - 1 page
 - b. ☒ Descriptive Title of the Invention
 - c. ☐ Cross References to Related Applications *(if applicable)*
 - d. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
 - e. ☐ Reference to Microfiche Appendix *(if applicable)*
 - f. ☒ Background of the Invention
 - g. ☒ Brief Summary of the Invention
 - h. ☐ Brief Description of the Drawings *(if applicable)*
 - i. ☒ Detailed Description
 - j. ☒ Claim(s) as Classified Below - 1 pages
 - k. ☒ Abstract of the Disclosure - 1 page
4. ☐ Drawing(s) *(when necessary as prescribed by 35 U.S.C. 113)* - _____ sheets _____ pages
5. ☐ Oath or Declaration _____ pages
- a. ☐ Newly executed *(original or copy)* ☐ Unexecuted
 - b. ☐ Copy from a prior application (37 C.F.R. 1.63(d)) *(for continuation/divisional appln only)*
6. ☐ Separate Power of attorney _____ pages
- ☐ 37 C.F.R. 3.73(B) Statement *(when there is an assignee and power of attorney is from assignee)*. It is hereby certified that the undersigned has authority to make this certification and has reviewed all the documents in the chain of title of the patent application identified herein and, to the best of undersigned's knowledge and belief, title is in the assignee identified in the accompanying Power of Attorney.
7. ☐ Incorporation by Reference *(usable if Box 5b is checked)*
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 5b, is considered as being part of the disclosure of the accompanying

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application and is hereby incorporated by reference therein.

8. ☒ Verified Statement(s) Claiming Small Entity Status _____ pages
- a. ☐ Independent Inventor
- b. ☐ Small Business Concern ("Assignee")
- c. ☐ Non-Profit Organization
- d. ☐ Non-Inventor Supporting Claim by Another
- e. ☐ A small entity statement was filed in the prior nonprovisional application and such status is still proper and desired.

9. ☐ Computer Program in Microfiche (*Appendix*) _____ pages

10. ☐ Nucleotide and/or Amino Acid Sequence Submission _____ pages
(*if applicable, all must be included*)
- a. ☐ Paper Copy
- b. ☐ Computer Readable Copy (*identical to computer copy*)
- c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

11. ☐ Assignment Papers: _____ pages
- a. ☐ Assignment Recordation Cover Sheet (Form PTO 1595)
- b. ☐ Assignment
- c. ☐ A check in the amount of \$_____ to cover the Recordal Fee
- d. ☐ Previously recorded on _____, Reel *, Frame *.

12. ☐ English Translation Document (*if applicable*) _____ pages

13. ☐ Information Disclosure Statement: _____ pages
- a. ☐ PTO Form 1449 b. ☐ Copies of IDS Citations

14. ☐ Preliminary Amendment _____ pages
- The fee calculation below is based on the claims after the preliminary amendment.

15. ☒ Acknowledgement Postcard - 1 page

16. ☒ Form of Mailing - Express Mail (*Specify Label No.*): EL015803975US

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17. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)* _____ pages

18. ☒ Additional Enclosures *(please identify below)*: _____ 1 page

☒ Constructive Petition for Extension of Time and Fee Authorization Pursuant to 37 C.F.R.
§1.136(a)(3)

☐ _____

Respectfully submitted,

VIDAS, ARRETT & STEINKRAUS

Date: 9/11/1998

By: _____

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DOCKET NO.: P52.2-7161

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
APPLICATION FOR UNITED STATES LETTERS PATENT**

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TITLE: *COMPOSITION FOR CREATING VASCULAR OCCLUSIONS*

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COMPOSITION FOR CREATING VASCULAR OCCLUSIONS

Background of the Invention

1. Field of the Invention

5 This invention relates to a composition used to treat arteriovenous malformations ("AVMs") and other vascular abnormalities. The composition includes a cyanoacrylate liquid monomer and gold in a prepolymerized polymer of cyanoacrylate. The composition is placed into the body lumen via standard catheter procedures or directly percutaneously.

2. Description of the Related Art

10 AVMs and vascular tumors, especially those of the brain, are exceedingly difficult to treat. These growths may occur all over the body, but are especially difficult to treat when in the brain or brain stem. The composition of the invention is especially useful in treating neurological AVMs, but may also be used to treat tumors anywhere in the body.

Cyanoacrylate adhesives have been used surgically but are limited in their usefulness by cytotoxicity and heat generation. The brain is unusually sensitive to cytotoxicity and heat.

20 The art described in this section is not intended to constitute an admission that any patent, publication or other information referred to herein is "prior art" with respect to this invention, unless specifically designated as such. In addition, this section should not be construed to mean that a search has been made or that no other pertinent information as defined in 37 C.F.R. § 1.56(a) exists.

Summary of the Invention

25 The invention provides a composition that may be placed in a body lumen including veins and arteries by super selective catheterization or direct puncture using standard tools of the interventional angiographer. The composition of the invention has been successfully tested in simulated models of the AVMs and tumors under fluoroscopy and in systems that closely resembles the neurological condition of the human body.

30

Further studies have been done in the pig rete. The rete is a body of fine arteries that allows the blood to flow into the pig brain which closely resembles normal human AVMs.

The composition is a cyanoacrylate which involves mixing two separate
5 containers of the material immediately prior to administration of the material into the AVM by catheter. The composition may contain seven ingredients which are divided into two parts prior to mixture and use. It furnishes properties that are useful for closing neurological AVMs. The product can also be used to close any growth resembling an AVM in any part of the body. Because of the sensitive nature of the tissues in the brain,
10 the general sensitivity of the product must be controlled. In less sensitive areas, the product will work equally as well.

Part I consists of a cyanoacrylate liquid monomer containing pure phosphoric acid (250 ppm) hydroquinone (100 ppm) and P-methoxyphenol (1200 ppm). This composition is stable and unchanging we believe for over two years. The container
15 in which Part I is stored requires cleaning and preparation before such stability can be achieved. The liquid monomer of choice for this usage is 2-hexyl cyanoacrylate.

Part II consists of pure powdered gold (5 ± 3 microns), a small amount of prepolymerized polymer of the same cyanoacrylate and ethyl myristate. Any of the large chain fatty acid esters will work to replace ethyl myristate so long as they are liquids.

20 The pre-polymerized polymers of cyanoacrylate are unstable and change their structures and properties even in the solid state. The change is exponential and therefore the polymer must be used within a limited amount of time before deterioration occurs.

The polymer is prepared by addition of part I to a rapidly stirring weak
25 bicarbonate-water solution. The addition must be added drop-wise to avoid unpolymerized masses from forming. The solid polymer is washed thoroughly with pure water to remove any traces of bicarbonate, then washed thoroughly with pure methanol to remove the water. Methanol dries rapidly and when the polymer is further dried at a high reduced pressure for 16 - 18 hours, it is considered dry. The polymer must be used in the
30 next step within 24 hours to obtain consistent results in the final product. This mixture must be sterilized within 72 hours from the time of preparation.

Part II is sterilized with ethylene oxide gas with the stopper held in an open position. Ethylene oxide is an alkylating agent and after sterilization the prepolymerized polymer is stable. Hence, the stability and sterilization of part 2 are carried out simultaneously. The sterilized samples of Part II are capped in a clean room under sterile handling conditions.

The pre-polymerized polymer can be stabilized by treatment with any of the strong alkylating agents, like ethylene oxide, ketene, etc.

This composition of matter has good cohesion as well as adequate adhesion to function well for AVMs and other similar uses within the vascular tree. The cohesion keeps the material together during the time required for it to polymerize. The adhesion makes it stick to the artery walls.

The polymerized device will cause a modest but desirable inflammatory response in the treated tissues.

A formulation for Arteriovenous Malformations and Tumors

It is desirable to prepare a formulation for the intravascular occlusion of AVMs and Tumors that will have the following properties:

- The product has a very slow rate of biodegradation.
- Both liquid and solid forms should have excellent cohesion.
- The delivered product should have medium adhesion
- The delivered product must be radiopaque.
- The solid polymer should be soft and pliable.
- The delivered product must have a very low or negligible histotoxicity.
- The deposited product must have no long term negative properties such as carcinogenicity, teratogenicity, systemic toxicity or other unpredictable biological and medical effects.
- The products must be sterile.
- The delivered product must have good flow characteristics for selective catheterization.

- The product must be stable on storage for an extended period of time.
- The formulation should be made from pure products and be reproducible for simple manufacturing procedures.

5

The product formulation is:

Part I (M1)	
2-Hexyl Cyanoacrylate	999,550 ppm
Hydroquinone	100 ppm
p-Methoxyphenol	100 ppm
Pure Phosphoric Acid	250 ppm
Part II (M2)	
Pure Gold	1.0000 g
Pure Ethyl Myristate	0.5000 g
FMS*	0.0200 g

* FMS is a specially prepared polymer of 2-hexyl cyanoacrylate and must be used within 24 hours of preparation or will change and be unusable. Further, it must be sterilized within 72 hours.

Each item of this formulation is critical to the proper performance of the product.

2-Hexyl Cyanoacrylate

This cyanoacrylate homolog was chosen because it biodegrades very slowly in blood or any living tissue. The secondary alcohol will biodegrade several thousand times slower than its primary derivative. This very slow degradation rate also lowers greatly the histotoxicity.

Hydroquinone

When the amount of hydroquinone is reduced by half (50 ppm) the product shows low shelf life stability. Large amounts over 100 ppm do not seem to effect the product stability. This inhibitor lowers the effect of the high energy free radicals that may appear in the cyanoacrylate

p-Methoxyphenol

The slow polymerization of cyanoacrylates even under refrigeration is caused by low energy free radicals. When 100 ppm of p-methoxyphenol is present this slow polymerization is prevented and long term stability is achieved. Less p-methoxyphenol (50 ppm) will not protect the product.

Sulfur Dioxide

The faintest trace of sulfur dioxide is present in the product. One part per million can be seen and less is present. However, this very faint trace adds to the stability of Neuracryl* ml in the ampule.

Gold

Tantalum, platinum and gold are all radiopaque. Gold was best for us because it could be suspended colloiddally in the mixture. One gram of gold is used per device.

Ethyl Myristate

Subbicates, fatty acid esters and other plasticizers, are useful for fastening the polymers of the cyanoacrylates. they also will stabilize the pre-formed polymers of the cyanoacrylates so that they may be used as thickeners. We have chosen ethyl myristate, an esterified, biocompatible fatty acid because of the convenience of purification and analysis and because it works well to give the formulation the desirable properties.

FMS

FMS is the polymer of 2-hexyl cyanoacrylate formed in a weak, aqueous sodium bicarbonate solutions. The polymer differs in structure and size depending on how it is formed. This polymer will remain stable until M2 can be formulated. The polymer must be formed and dried completely before use. The final formulation of M2 must occur within 24 hours because the ethyl myristate stabilized FMS until sterilization can be performed. After sterilization the product is stable for several years.

Neuracryl M

M1 and M2 are mixed immediately before use. The mixture should be used within 4 hours after mixing. If there is a delay, the syringe should be turned over several times a minute to resuspend the gold which will be settled.

WHAT IS CLAIMED IS:

1. A composition for creating vascular occlusions in an animal comprising a mixture of:

(a) Part 1 comprised of 2-hexyl cyanoacrylate, hydroquinone, p-methoxyphenol and phosphoric acid; and

(b) Part 2 comprising gold metal, ethyl myristate and FMS.

2. The composition of Claim 1 wherein Part 1 includes about 100 PPM hydroquinone, 100 PPM p-methoxyphenol, 250 PPM phosphoric acid and the remainder 2-hexyl cyanoacrylate.

3. The composition of Claim 2 wherein Part 2 includes about 65 percent gold, about 30 percent ethyl myristate and the remainder FMS.

4. The composition of Claim 3 wherein FMS is a sterilized polymer of 2-hexyl cyanoacrylate in an aqueous bicarbonate solution.

5. The composition of Claim 1 wherein Part 2 includes sulfur dioxide as a stabilizer.

6. A method for creating vascular occlusions in an animal needing occlusion comprising the steps of :

(a) Mixing together Part 1 comprised of 2-hexyl cyanoacrylate, hydroquinone, p-methoxyphenol and phosphoric acid with Part 2 comprising gold metal, ethyl myristate and FMS; and

(b) injecting the mixture into a vascular site needing occlusion with the gold metal suspended in the mixture.

COMPOSITION FOR CREATING VASCULAR OCCLUSIONS**Abstract of the Disclosure**

5 A composition including 2-hexyl cyanoacrylate and gold is useful in treating arteriovenous malformations (AVMs) and other body lumens to be blocked.